

## Charge fluctuations and their effect on conduction in biological ion channels

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# Charge fluctuations and their effect on conduction in biological ion channels

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**Abstract.** The effect of fluctuations on the conductivity of ion channels is investigated. It is shown that modulation of the potential barrier at the selectivity site due to electrostatic amplification of charge fluctuations at the channel mouth exerts a leading-order effect on the channel conductivity. A Brownian dynamical model of ion motion in a channel is derived that takes into account both fluctuations at the channel mouth and vibrational modes of the wall. The charge fluctuations are modeled as a shot noise flipping the height of the potential barrier. The wall fluctuations are introduced as a slow vibrational mode of the protein motion that modulates ion conductance both stochastically and periodically. The model is used to estimate the contribution to the conductivity of ion channels coming from the electrostatic amplification of charge fluctuations.

**Keywords:** dynamics (theory), diffusion

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**1. Introduction**

Ion transport through the channels in cellular membranes underlies all electrical signal transduction and processing by living organisms. Accordingly ion channels, being natural nanotubes, control a vast range of biological functions in health and disease. The understanding of their structure–properties relationship is the subject of intensive, ever-growing, fundamental and applied research in biology, physics, and nanotechnology [1, 2]. A central problem in studies of ion permeation through biological membrane channels is to understand how channels can be both highly selective between like ions and yet still conduct millions of ions per second [3]. Indeed, selectivity between ions of the same charge implies that there exists a deep potential well for conducting type ions at the selectivity site of the channel. On the other hand such channels can pass up to  $10^8$  ions per second [4] corresponding to almost free diffusion.

Significant progress has been made towards an understanding of this problem over the last few decades. In particular, the molecular structure of the KcsA potassium channel [5] that discriminates between  $\text{Na}^+$  and  $\text{K}^+$  was determined by crystallographic analysis. Furthermore, by detecting the size of the structural fluctuations [6] and conformational changes [7], it has become possible to provide the experimental information needed for molecular modeling of the dynamical features of the observed selectivity and gating [8, 9]. In particular, the minimum radius of the selectivity filter in KcsA is  $\sim 0.85 \text{ \AA}$ , which is to be compared with  $1.33 \text{ \AA}$  for the ionic radius of  $\text{K}^+$ , suggesting that flexibility of the filter is coupled to ionic translocation [10]. It has therefore become apparent that fluctuations in the channel walls play a fundamental role in maintaining high conductivity in highly selective channels (see also Elber [11]).

Another important source of modulation of the electrostatic potential identified in earlier research [12, 13] relates to the interaction of the ion in the channel with charge fluctuations in the bath solutions. The effect of current fluctuations and noise on the channel entrance rates and on the channel conductivity was also considered in [14, 15]. It becomes clear that fluctuations of the electrostatic potential within ion channels induced by various sources may provide a key to the solution of the central problems of permeation

and selectivity. Models of such fluctuations have thus a central role in research on the permeability of ion channels. It is important to note that dynamical models of ion motion in the channel can also provide a link between studies of the permeability of open channels and channel gating. Notwithstanding recent advances, theoretical modeling of the dynamical features of ion channels is still in its infancy. In particular, little is yet known about the relative importance of the different dynamical mechanisms and sources of fluctuations in the ion channels.

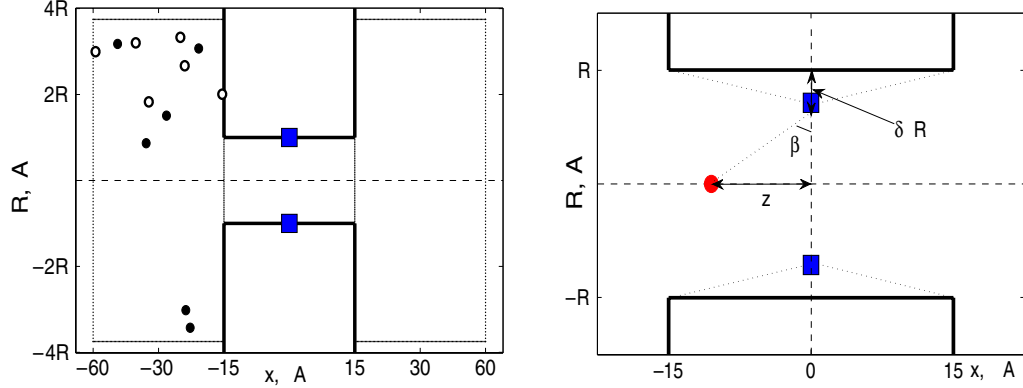
In our earlier work we started to develop a dynamical model [16]–[21] of ionic conductivity through open channels. It takes into account the coupling of ion motion to vibrations of the wall [16, 17] and to charge fluctuations at the channel mouth [19, 20]. Our goal is to derive a self-consistent model that allows for analytical estimation of the potential barrier at the selectivity site and for the effects of fluctuations on the conductivity of the channels. The starting point of our approach is a self-consistent quasi-analytical solution of the Poisson and Nernst–Planck equations in the channel, and in the bulk [21], allowing for accurate estimation of the current–voltage characteristics of ion channels [22] (see also [23]–[27]). The electrostatic channel potentials resulting from these estimates can be further used to estimate the relative contributions to the channel conductivity from the different sources of fluctuations.

In this paper we introduce a model of ion permeation that takes into account the dynamical effect of the charge fluctuations through the resultant shot noise, and we demonstrate that the latter has a leading-order effect on the transition probabilities. We show that charge fluctuations at the channel mouth can be modeled as a flipping of the electrostatic potential at the selectivity site, which fluctuates between two maximum values at a rate corresponding to the random arrivals of ions at the channel mouth. The theoretical framework developed will allow us in the future to include into the model the modulation of the potential at the selectivity site due to hydration effects inside the channel.

A model of 3D Brownian dynamics simulation of ions in the bulk and inside the channel is described in section 2. Using results of the 3D simulations in the bulk we present in section 3 a reduced model of an ion moving in the channel and interacting with the wall vibrational modes and with charge fluctuations at the channel entrance. The model uses the channel potential derived from a self-consistent solution of the Poisson equation and the flipping rates of the potential barrier obtained from simulations of Brownian motion of ions in the bulk. In section 4, we estimate analytically the mean first-passage time of the channel. These estimates are based on the assumption that barrier crossing and barrier fluctuations are correlated for a general form of the potential barrier [28]. The mean first-passage time is calculated as a weighted sum of the escape time  $\tau_-$  over the low barrier  $\Delta E_0$ , and the escape time  $\tau_+$  over the high barrier  $\Delta E_1$ . The results are compared with single-channel data in section 5. Conclusions are drawn and future directions of research are outlined in section 6.

## 2. Brownian dynamics simulations in the bulk and inside the channel

We consider the following Brownian dynamical model of the ion permeation (see the sketch in figure 1 (left)). The system is comprised of three compartments of equal size. The middle block represents the protein, through which there is a cylindrical hole



**Figure 1.** Left: sketch of the model. The middle block represents the protein, through which there is a cylindrical hole approximating the open ion channel. The moving charged segment of the protein wall, assumed elastically bound to the wall, is shown by the filled squares. Negative ions are shown by the filled circles, and positive ions by the open circles. Right: sketch of an ion moving along the channel axis. The conducting ion is shown by a red circle. The difference between ion coordinate  $x$  and location of the selectivity site  $x_{ss}$  is  $z$ . The vertical displacement of the selectivity site is  $\delta R$ . The angle between a line connecting the ion with the selectivity site and the vertical axis is  $\beta$ .

approximating the open channel. To model the ion's coupling to the vibrational modes of the channel, we introduce a moving segment of the protein wall that is elastically bound to the wall. The moving segment is charged and represents the selectivity site. The dynamics of the ions in the bath and channel, and of the moving segment, are modeled using Brownian dynamics (BD) simulations; see equations (2)–(5) coupled to the Poisson equation (1).

$$-\nabla \cdot (\varepsilon(\vec{r}) \nabla \phi(\vec{r})) = \rho(\vec{r}), \quad (1)$$

$$m_i \ddot{\vec{x}}_i + m_i \gamma_i \dot{\vec{x}}_i = \vec{F}_{C,i} + \vec{F}_{sr,i} + \vec{F}_{H,i} + \sqrt{2m_i \gamma_i k_B T} \vec{\xi}_i(t), \quad (2)$$

$$m_j \ddot{\vec{x}}_j + m_j \gamma_j \dot{\vec{x}}_j = \vec{F}_{C,j} + \vec{F}_{sr,j} + \vec{F}_{H,j} + \sqrt{2m_j \gamma_j k_B T} \vec{\xi}_j(t), \quad (3)$$

$$m \ddot{x} + m \gamma \dot{x} = F_C + F_{ch} + F_{iw,i} \sin(\beta) + \sqrt{2m \gamma k_B T} \xi(t), \quad (4)$$

$$M \delta \ddot{R} + M \Gamma \delta \dot{R} + K \delta R = F_{iw,M} \cos(\beta) + \sqrt{2M \Gamma k_B T} \nu(t). \quad (5)$$

Here  $\vec{r}_{ij} = \vec{x}_i - \vec{x}_j$ ,  $r_{ij} = |\vec{r}_{ij}|$ ; and  $m_i$ ,  $\vec{x}_i$  and  $q_i$ ,  $m_i \gamma_i$  and  $\sqrt{2m_i \gamma_i k_B T} \vec{\xi}_i(t)$  are the mass, position, charge, friction coefficient and the stochastic force of or on the  $i$ th ion. The distance between ions  $i$  and  $j$  is  $r_{ij}$ . For simplicity, we restrict the analysis to two types of ion: the index  $i$  will correspond to  $\text{Na}^+$ , while index  $j$  corresponds to  $\text{Cl}^-$ . The motion of the charged residual of mass  $M$  at the selectivity site is characterized by the displacement  $\delta R$  in the vertical direction from the equilibrium position  $R$  and an elastic force  $\propto K \delta R$ . Note that, in general, values of the effective mass and diffusion constant  $D$  of the ion moving within the channel may deviate from the corresponding values in bulk due to the non-trivial effect of hydration in the channel. Coupling between the motion of the ion in

the channel and the normal mode of the wall oscillations is accounted for by the term  $F_{iw}$  corresponding to the Coulomb interaction between ion and charge at the selectivity site. Retaining only the axial component of the force for the ion motion in the channel, and the radial component of  $F_{iw}$  for the oscillating wall, we have

$$F_{iw,i} = \frac{Qq_j}{4\pi\epsilon\epsilon_0 d^2} \frac{z}{d}, \quad F_{iw,M} = \frac{Qq_j}{4\pi\epsilon\epsilon_0 d^2} \frac{\delta R}{d}.$$

Here  $d = \sqrt{((R + \delta R)^2 + z^2)}$ ,  $z = x - x_{ss}$  where  $x$  is the coordinate of the ion in the channel, measured along the channel axis, and  $x_{ss}$  is the location of the selectivity site. An additional coupling of the ion motion to fluctuations of the channel wall is effected via modulation of the channel potential by the moving wall. This is taken into account through the term  $F_{ch}$  in equation (4). The ions in the bulk (see equations (2), (3)) do not feel the channel potential. Instead, their motion is governed by the Coulomb interaction  $F_C$ , by the short-range interaction  $F_{sr}$ , and by hydration forces  $F_H$  [3]:

$$\begin{aligned} \vec{F}_{C,i} &= \sum_{j=1}^N \frac{q_i q_j}{4\pi\epsilon\epsilon_0 r_{ij}^2} \frac{\vec{r}_{ij}}{r_{ij}}, & \vec{F}_{sr,i} &= \sum_{j=1}^N \frac{9U_0 R_c^9}{r_{ij}^{10}} \frac{\vec{r}_{ij}}{r_{ij}}, \\ \vec{F}_{H,i} &= \sum_{j=1}^N \left[ AU_0 \exp\left(\frac{R_{ij} - r_{ij}}{a_e}\right) \sin\left(2\pi \frac{R_{ij} - r_{ij}}{a_w} - \alpha\right) \right] \frac{\vec{r}_{ij}}{r_{ij}}, \end{aligned}$$

where  $A = \sqrt{1 + (a_w/2\pi a_e)^2}$  and  $\alpha = \arctan(a_w/2\pi a_e)$ .

The effect of the surroundings is taken into account by the average frictional force with friction coefficient  $m_i \gamma_i$  and a stochastic force  $\sqrt{2m_i \gamma_i k_B T} \vec{\xi}_i(t)$ . The addition of the pairwise repulsive  $1/r^9$  soft-core interaction potential ensures that ions of opposite charge, attracted by the inter-ion Coulomb force, do not collide and neutralize each other.  $U_0$  and  $R_c$  are respectively the overall strength of the potential and the contact distance between ion pairs. The oscillating part, added to the potential, takes explicit account of the internuclear separation for the two solvents, where  $a_w$  is the oscillation length,  $a_e$  is the exponential drop parameter, and  $R_{ij}$  is the origin of the hydration force which is shifted from  $R_c$  by  $+0.2 \text{ \AA}$  for like ions and by  $-0.2 \text{ \AA}$  otherwise [29].  $F_{ch}$  is the dielectric force in the channel, obtained by solving Poisson's equation numerically using finite volume methods (FVM) [30]. We use the Langevin equation to model the collective motion of the atoms forming the channel protein's charged ring located at the selectivity filter. In this way, our analysis is based on the assumption that the movement of structural domains of the channel protein may be described as the motions of independent, elastically bound Brownian particles [31]. We have included the damping term  $M\Gamma\delta\dot{R}$  and the corresponding random force  $\sqrt{2M\Gamma k_B T} \nu(t)$ , whose amplitude is related to the damping constant via the fluctuation-dissipation theorem. The function  $\nu(t)$  is a Gaussian white noise.  $Q$  is the total fixed charge on the flexible ring interacting with an ion of charge  $q_j$  on the channel axis  $z$ .  $R$  is the channel radius,  $\delta R$  is a small variation of the channel radius and  $K$  is the elastic constant of the channel protein. In the particular case of the Gramicidin A (GA) channel, the value of the elastic constant is estimated by calculating the root mean square deviation (RMSD) of the backbone forming its central part, together with the single-ion potential of a  $\text{Na}^+$  ion as it traverses the channel. Using data from [32], we obtain an elastic constant of  $\sim 1.66 \text{ N m}^{-1}$  for a maximum RMSD of  $1 \text{ \AA}$ . The GA channel molecular weight  $M$  is about  $4 \text{ kDa} = 6.64 \times 10^{-24} \text{ kg}$  [33]. The diffusion constant

**Table 1.** Parameters used in the calculation of the short-range ion–ion interaction with hydration.

Ions	$U_0$ ( $k_B T$ )	$R_c$ (Å)	$R$ (Å)	$a_w$ (Å)	$a_e$ (Å)
Na–Na	0.5	3.50	3.7		
Na–Cl	8.5	2.76	2.53	2.76	1.4
Cl–Cl	1.4	5.22	5.42		

of the protein in the membrane is between  $10^{-14}$  and  $10^{-16}$   $\text{m}^2 \text{s}^{-1}$  [34]. The parameters of the ion–ion interaction are presented in table 1. Other parameters used in the simulations are: dielectric constants  $\varepsilon_2 = 80$ ,  $\varepsilon_1 = 2$ ; masses (kg)  $m_{\text{Na}} = 3.8 \times 10^{-26}$ ,  $m_{\text{Cl}} = 5.9 \times 10^{-26}$ ; diffusion coefficients ( $\text{m}^2 \text{s}^{-1}$ )  $D_{\text{Na}} = 1.33 \times 10^{-9}$ ,  $D_{\text{Cl}} = 2.03 \times 10^{-9}$  (where  $D$  is related to the friction coefficient via  $D = (k_B T / m\gamma)$ ); ion radii (Å)  $r_{\text{Na}} = 0.95$ ,  $r_{\text{Cl}} = 1.81$ ; temperature (K)  $T = 298$ .

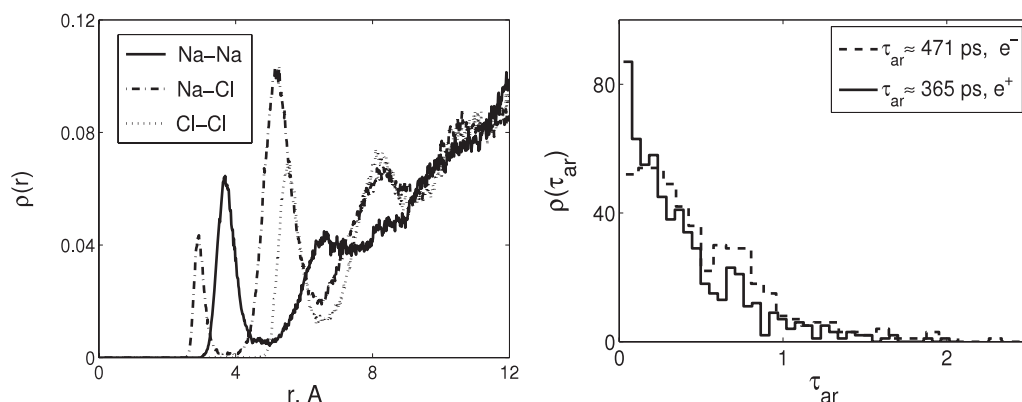
### 3. Reduced model for ion channel conduction

To derive the reduced model we note that equations (1)–(5) correspond to a many-body problem with widely varying timescales, ranging from ps (ion fluctuations) to ns (wall vibrations). We further assume that the channel is occupied most of the time by only one ion, and that the rate of transition of ions through the channel is mainly determined by escape over the potential barrier at the selectivity site. Thus the effect of the many-body ion dynamics in the bulk on the ion motion in the channel is twofold: (i) delivery of ions to the channel mouth and (ii) modulation of the channel potential by the charge fluctuations at the channel mouth. Under these physiologically plausible assumptions one can separate the ion motion in the channel from the many-body ion dynamics in the bulk. The resulting equations of ion dynamics in the channel coupled to the wall fluctuations can be written as follows:

$$m\gamma\dot{x} = -\frac{dV(x,t)}{dx} + \sqrt{2m\gamma k_B T} \xi(t), \quad (6)$$

$$M\delta\ddot{R} + M\Gamma\delta\dot{R} + K\delta R = F_{iw,M} \cos(\beta) + \sqrt{2M\Gamma k_B T} \nu(t). \quad (7)$$

Note that the reduced motion of the conducting ion is overdamped, whereas the wall fluctuations are damped. The damped vibrational mode models the relatively slow (on a timescale of ns) motion of the protein of the channel walls that was suggested [35, 12] to be essential for the ion transport process. The potential  $V(x,t)$  in our approximation is made up of three main contributions: (i) the potential of Coulomb interaction with ions in the bulk solution  $V_C$ ; (ii) the electrostatic potential induced by interaction with the channel protein  $V_{\text{ch}}$ ; (iii) the potential of Coulomb interaction with the wall charge at the selectivity site. By an averaging procedure, the effect of multi-ion motion in the bulk solutions is reduced to the Coulomb interaction with ions arriving at the channel mouth. The later process can be viewed as a stochastic Poisson process or as shot noise that modulates the potential barrier for the conducting ion at the selectivity site. Our goal is to estimate analytically the effect of this potential modulation on the channel conductivity, as will be discussed in detail in the next section.



**Figure 2.** Simulations of Brownian dynamics in the bulk liquid. Left: the number of ions as a function of the distance between ions of different types:  $C = 400$  mmol; box size:  $40$  Å. Forces included in the simulations were: (i) Coulomb interaction; (ii) short-range repulsion; (iii) hydration. Right: the arrival time distribution for positives (solid line) and negative (dashed line) for cylindrical channel of radius  $r = 6$  Å.

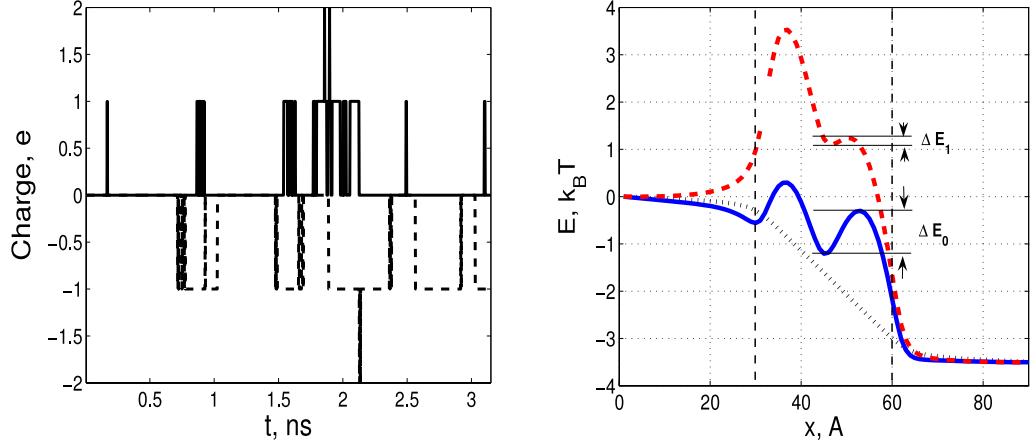
To quantify the effect of multi-ion motion in the bulk on the conducting ion at the selectivity site, we have simulated the ion's Brownian dynamics. The resulting ion-ion distributions in the bulk are shown in figure 2 (left). We emphasize that these distributions are very close to those obtained earlier in both BD simulations [3] and experiments [36]. The arrival time distributions for  $\text{Na}^+$  and  $\text{Cl}^-$  ions at the channel mouth (defined as a cylindrical section of radius  $R$  and length  $R$ ) obtained in our simulations are shown in figure 2 (right). Note that these distributions are exponential for both  $\text{Cl}^-$  and  $\text{Na}^+$  with mean arrival times  $\tau^- = 471$  ps and  $\tau^+ = 365$  ps respectively. These estimates are in agreement with the theoretical estimates in [37]:

$$\tau_{\text{arrival}} = \frac{1}{2\pi cDR}, \quad (8)$$

where  $c$  is the ion concentration. The time evolution of the charge in the channel mouth is shown in figure 3 (left). It can be seen that the charge at the channel mouth is a Poisson process with the three main states being  $+1e$ ,  $0$ , and  $-1e$ . As a first approximation it is convenient to divide the states of the channel potential affected by the charge fluctuations into two effective states: (i) a state of high conductivity, corresponding to  $+1e$ ; and (ii) two states of low conductivity, corresponding to  $0$  or  $-1e$  at the channel mouth. In this approximation the effect of having three states of the potential is taken into account by asymmetry of the transition rates between the two effective states. The corresponding transition rates can be estimated as  $\alpha^\pm = 1/\langle T_\pm \rangle$ , where  $\langle T_\pm \rangle$  are mean residence times of two effective states, giving  $(\alpha^+)^{-1} = 0.22$  and  $(\alpha^-)^{-1} = 0.38$  ns. The occupation probabilities of these two states are 0.36 and 0.64 respectively. The effect of the wall oscillations on the channel potential was estimated earlier [20] and for simplicity the wall will be assumed rigid in the rest of the paper.

To estimate the effect of charge fluctuations on the value of the channel potential we solve the Poisson equation for various positions of the conducting ion along the channel axis in two cases: (i) when there are no other ions at the channel entrances; (ii) when there





**Figure 3.** Left: charge fluctuations at the channel mouth. Positive charge is shown by the solid line and negative charge by the dashed one. Right: the potential energy profiles as a function of the position of the ion when: the first ion is fixed at the channel mouth (dashed line) and the second is moving along the channel axis. The solid line corresponds to the potential energy of a single ion moving on the channel axis, and the dotted line to the potential energy of the passive channel. The vertical dashed lines show the channel entrance and exit. The height of the potential energy barrier seen by a single ion at the selectivity site as it moves from the left-hand side to the right-hand side of the channel is denoted as  $\Delta E_0$ . In the presence of a second ion at the channel's left mouth this barrier is reduced to  $\Delta E_1$ .

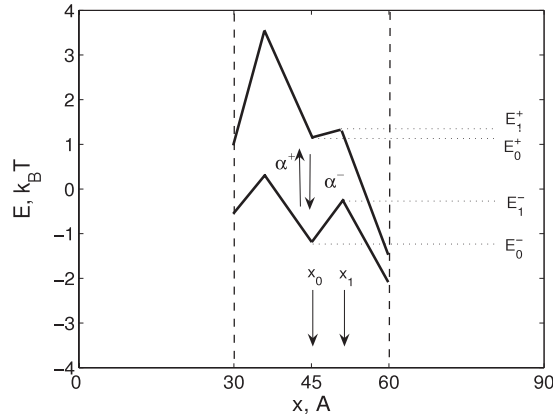
is one positive ion at the left entrance to the channel. The results of these calculations are shown in figure 3 (right). The low conductivity effective state of the channel is shown by the blue solid line and corresponds to the potential barrier  $\approx 1k_B T$  at the selectivity site. The high conducting state is shown by the dashed line and corresponds to a potential barrier height  $\approx 0.2k_B T$ , i.e. practically no barrier state. It can be seen that the charge fluctuations are enhanced in channels of low dielectric constant, resulting in strong modulation of the potential barrier at the selectivity site [20] (see also [38]). It is therefore possible to build a simple model capable of coupling the motion of ions in the channel to the bath solution. The channel potential becomes

$$V(x, t) = \frac{V_+ + V_-}{2} + \frac{V_+ - V_-}{2} \chi(t), \quad \chi(t) = \pm 1, \quad (9)$$

$$V_+ = \frac{\Delta E_1}{x_m} (x - x_0) + E_0^+, \quad V_- = \frac{\Delta E_0}{x_m} (x - x_0) + E_0^-,$$

where  $\chi(t)$  is a Poisson random force with two rates of transition  $\alpha_{\pm}$  between the states  $+1$  and  $-1$ . The charge fluctuations at the channel mouth thus result in flipping of the potential. Here  $\Delta E_0 = E_1^- - E_0^-$  and  $\Delta E_1 = E_1^+ - E_0^+$ , with  $\Delta E_0 > \Delta E_1$  are respective barriers of the potential in two states, and  $x_m = x_1 - x_0$ .

A direct analogy can be made between the model described by equation (6) and the model described by Zürcher [28] whose barrier fluctuation is controlled by a dichotomic noise of zero mean and exponential correlation. An approximation of the fluctuating



**Figure 4.** Approximation of the fluctuating potential.

potential is sketched in figure 4. The similarity of the two problems suggests that there is some possibility of semi-analytical estimations of the effect of the charge fluctuations.

#### 4. Estimation of the mean channel crossing time

We are interested in the transition of a particle initially trapped at the channel selectivity filter. This corresponds to the motion of the ion across the interval  $[x_0, x_1]$ . The approximate potential in this interval is given by (9). We are interested in unidirectional current, so there is no backward flow of ions. We assume that, on average, the channel is always occupied by a single  $\text{Na}^+$  ion. This arises from the fact that, when an ion is sitting in the middle of the channel, it is almost impossible for a second ion to enter the channel due to the height of the barrier at the left entrance of the channel, as can be seen from figure 4.

As a first approximation, we assume that the mean first-passage time (MFPT) is only determined by escape. Therefore the MFPT for the channel is expected to be a function of the two times  $\tau_+$  and  $\tau_-$  corresponding to the times of escape from the potential minimum in two effective states of the potential. Our derivation follows very closely the earlier discussion by Zürcher [28] with the difference that, here, we are interested in the asymmetric case with two transition rates.

Assuming no backflow, the quantities  $\tau_{\pm}(x)$  are defined [39] by

$$\frac{-1}{m\gamma} \frac{dV_+}{dx} \frac{d\tau_+}{dx} + \frac{k_B T}{m\gamma} \frac{d^2\tau_+}{dx^2} - \alpha^+ \tau_+ + \alpha^- \tau_- = -p_+, \quad (10)$$

$$\frac{-1}{m\gamma} \frac{dV_-}{dx} \frac{d\tau_-}{dx} + \frac{k_B T}{m\gamma} \frac{d^2\tau_-}{dx^2} - \alpha^- \tau_- + \alpha^+ \tau_+ = -p_-. \quad (11)$$

The potential jumps between positive and negative values, with respective rates  $\alpha^+$  and  $\alpha^-$ .  $p_{\pm}$  are the occupation probabilities of these states. We choose a reflecting boundary condition (BC) at the bottom of the barrier  $x = x_0$  and an absorbing BC at the top of the barrier  $x = x_1$ ,

$$\frac{d\tau_{\pm}(x = x_0)}{dx} = 0, \quad \tau_{\pm}(x = x_1) = 0, \quad (12)$$

with  $\tau_+$  and  $\tau_-$  specified, and the mean exit time of the Brownian particle initially trapped at the selectivity filter  $x = x_0$  is given by

$$\tau = \tau_+(x_0) + \tau_-(x_0). \quad (13)$$

Following Zürcher [28], the calculation of  $\tau_{\pm}$  is straightforward. We introduce

$$E = \frac{\Delta E_1 + \Delta E_0}{2}, \quad \Delta = \frac{\Delta E_1 - \Delta E_0}{2}, \quad (14)$$

and

$$\sigma(x) = \alpha^+ \tau_+(x) + \alpha^- \tau_-(x), \quad \delta(x) = \alpha^+ \tau_+(x) - \alpha^- \tau_-(x). \quad (15)$$

We find the coupled differential equations

$$\frac{-DE}{x_m k_B T} \frac{d\sigma}{dx} + D \frac{d^2\sigma}{dx^2} + (\alpha^+ p_+ + \alpha^- p_-) = (\alpha^+ p_+ - \alpha^- p_-) \delta + \frac{D\Delta}{x_m k_B T} \frac{d\delta}{dx}, \quad (16)$$

$$\frac{-DE}{x_m k_B T} \frac{d\delta}{dx} + D \frac{d^2\delta}{dx^2} - (\alpha^+ p_+ + \alpha^- p_-) \delta + (\alpha^+ p_+ - \alpha^- p_-) = \frac{D\Delta}{x_m k_B T} \frac{d\sigma}{dx}, \quad (17)$$

where  $D = D_{Na}$ , and the boundary conditions

$$\sigma(x = x_1) = 0, \quad \frac{d\sigma(x = x_0)}{dx} = 0, \quad \delta(x = x_1) = 0, \quad \frac{d\delta(x = x_0)}{dx} = 0. \quad (18)$$

We introduce the following scaled dimensionless coordinate:

$$x = \frac{x_m k_B T}{E} y. \quad (19)$$

The model is therefore characterized by the following parameters:

$$\tau_0 = 2 \frac{(x_m k_B T)^2}{DE^2}, \quad \eta = \frac{\Delta}{E}, \quad \lambda = \frac{\tau_0}{2} (\alpha^+ p_+ + \alpha^- p_-), \quad \beta = \frac{\tau_0}{2} (\alpha^+ p_+ - \alpha^- p_-). \quad (20)$$

The coupled differential equations then read

$$-\frac{d\sigma}{dy} + \frac{d^2\sigma}{dy^2} + \lambda = \beta\delta + \eta \frac{d\delta}{dy}, \quad (21)$$

$$-\frac{d\delta}{dy} + \frac{d^2\delta}{dy^2} - \lambda\delta + \beta = \eta \frac{d\sigma}{dy}, \quad (22)$$

and  $\sigma(y)$  and  $\delta(y)$  are subject to the BC

$$\sigma(y = y_1) = 0, \quad \frac{d\sigma(y = y_0)}{dy} = 0, \quad \delta(y = y_1) = 0, \quad \frac{d\delta(y = y_0)}{dy} = 0. \quad (23)$$

The solution of this system gives

$$\delta(y) = \sum_{i=1}^3 a_i \exp(q_i y) + \frac{(\beta - \lambda\eta)}{(\lambda - \beta\eta)}. \quad (24)$$

The eigenvalues  $q_i$  follow from

$$\begin{aligned} q_1 + q_2 + q_3 &= 2, \\ q_1 q_2 + q_2 q_3 + q_3 q_1 &= 1 - \lambda - \eta^2, \\ q_1 q_2 q_3 &= -(\lambda - \beta\eta). \end{aligned} \quad (25)$$

The  $a_i$  are given as follows:

$$\begin{aligned} a_1 &= -\frac{\beta - \lambda\eta}{D_s(\lambda - \beta\eta)} \left( q_3(q_2^2 - \lambda) - q_2(q_3^2 - \lambda) \right) \exp((q_3 + q_2)y_0) \\ &\quad - \frac{1}{D_s} \left( \frac{\lambda(\beta - \lambda\eta)}{\lambda - \beta\eta} - \beta \right) (q_3 \exp(q_3 y_0 + q_2 y_1) - q_2 \exp(q_3 y_1 + q_2 y_0)). \end{aligned} \quad (26)$$

Here  $a_2$  and  $a_3$  are determined by cyclic permutation of the indices of the  $q_i$  from  $a_1$ , and  $D_s$  is given by

$$D_s = q_1 q_2 (q_2 - q_1) (q_3 - 1) \exp((q_1 + q_2)y_0 + q_3 y_1) + \text{cyclic permutations}. \quad (27)$$

At  $y_0$ , we have

$$\begin{aligned} \sigma(y_0) &= \frac{1}{\eta} \sum_{i=1}^3 a_i \left[ \left( -1 + q_i - \frac{\lambda}{q_i} \right) \exp(q_i y_0) - \left( q_i - \frac{\lambda}{q_i} \right) \exp(q_i y_1) \right] \\ &\quad - \frac{(\beta - \lambda\eta)}{\eta(\lambda - \beta\eta)} + \left[ \frac{\lambda(\beta - \lambda\eta)}{\eta(\lambda - \beta\eta)} - \frac{\beta}{\eta} \right] (y_1 - y_0). \end{aligned} \quad (28)$$

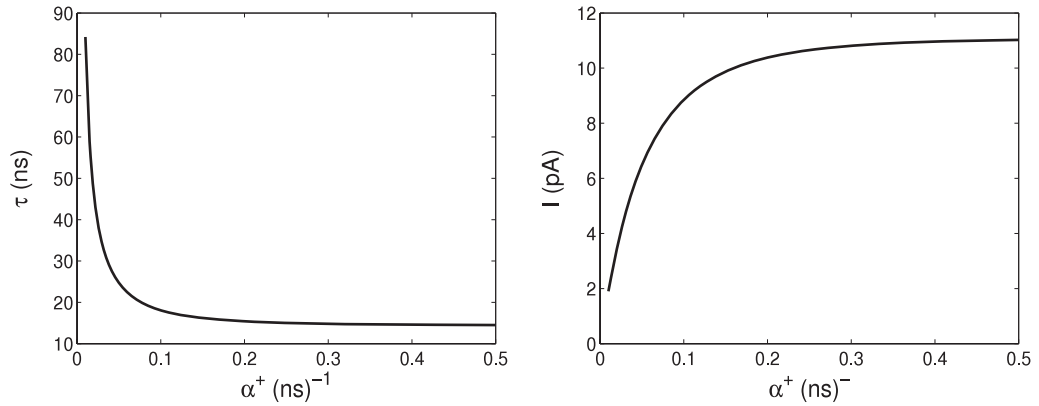
Combining equations (13) and (15), the mean exit time for the Brownian particle follows:

$$\tau = \frac{\sigma(y_0) + \delta(y_0)}{2\alpha^+} + \frac{\sigma(y_0) - \delta(y_0)}{2\alpha^-}. \quad (29)$$

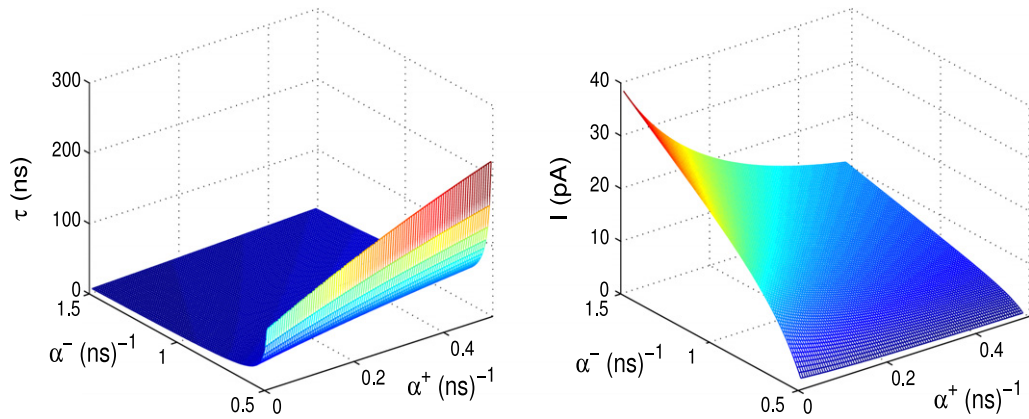
The effect of shot noise on ion channel conduction is related to the arrival of ions at the channel's mouth. We calculated the channel MFPT as a function of the two flipping rates. Since the channel has a high affinity for the ions and therefore slows them down, we have used a smaller ion diffusion coefficient inside the channel equal to  $1.33 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ . The results of the calculations are shown in figures 5 and 6. It is clear from figure 5 that the particle takes longer to cross  $\Delta E_0$  as compared to  $\Delta E_1$ . There is a fast drop in MFPT as the flipping rate  $\alpha^+$  increases. The current  $I = e/\tau$  is also presented as a function of  $\alpha^+$ . A more general view of the dependence of the MFPT and the current on the two rates is shown in figure 6. We emphasize that the transition rates obtained are essentially non-equilibrium. In particular, a current saturation effect can be observed as  $\alpha^+$  increases for a wide range of parameters. This is in accord with the experimental observation [33] of current saturation at high concentrations.

## 5. Comparison with experiment

We have compared the results of our calculations directly with the single-channel measurements of Andersen *et al* [33]. In order to estimate the current-concentration dependence, we used equation (8), an approximation calculated in the bulk in the absence of an electric field. As explained above, the arrival time given by this formula is comparable with that obtained from numerical simulations. It is the inverse of the flipping rate, which

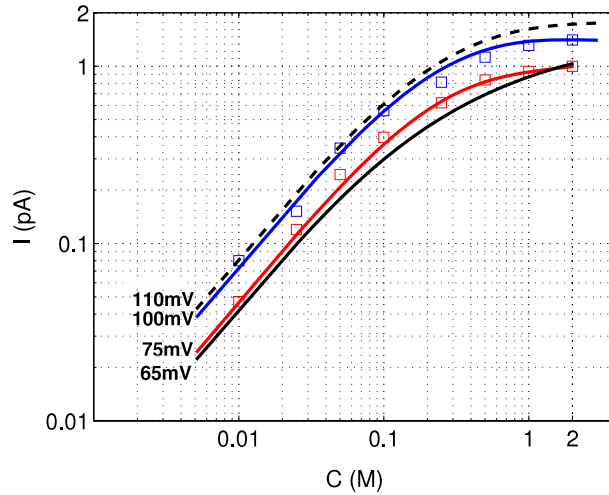


**Figure 5.** Left: MFPT as a function of  $\alpha^+$ . Right: current as a function of  $\alpha^+$ .



**Figure 6.** Left: MFPT as function of  $\alpha^+$  and  $\alpha^-$ . Right: current as function of  $\alpha^+$  and  $\alpha^-$ .

is proportional to the concentration. By varying the flipping rate, we correspondingly vary the concentration and are thus able to calculate the current as a function of the concentration. When the applied voltage increases, the second energy barrier, close to the channel's right-hand mouth, vanishes, thus invalidating our model. We therefore limit ourselves to low applied voltages. The ion diffusion coefficient and the two flipping rates are used as fitting parameters. With a careful choice of the diffusion coefficient as well as the range of variations of the positive and negative flipping rates it is possible to fit experiments as shown in figure 7. Although the range of experimental conditions under which the theory can fit experimental data is limited at present by a number of simplifying assumptions, these preliminary results are very encouraging. Furthermore, our model of the knock-on mechanism of conductivity may shed new light on the role of the effective dielectric constant within the channel and the importance of the additional charged sites at the channel mouth. Indeed, the effective dielectric constant of the channel not only affects the dielectric self-energy, as was extensively discussed earlier [23, 29, 32], but also has a leading-order effect on the amplification of the charge fluctuations in the channel. On the other hand, the existence of the additional sites outside the selectivity filter not only can reduce the potential barrier for the ion entering the channel [29], but also can



**Figure 7.** Current as a function of  $\text{Na}^+$  ionic concentration in a Gramicidin channel. The data points for the potential differences 75 and 100 mV are taken from the single-channel measurements of Andersen *et al* [33]; the curves are from theory for the parameter values given in the text.

modify substantially the flipping rates of the potential barrier due to charge fluctuations and therefore the dependence of the channel conductivity on the bulk concentrations. These and other features of the proposed model, including the effect of a more realistic potential profile on the channel conductivity, will be investigated in more detail elsewhere.

## 6. Conclusion

In summary, we have introduced a Brownian dynamical model of ionic transitions through a channel, taking into account charge fluctuations at the channel mouth and the fluctuations of the channel walls. The statistical properties of the charge fluctuations were reconstructed from 3D Brownian dynamics simulations of multi-ion motion in the bulk solution. It was shown that distributions of ion arrival times at the channel mouth are exponential. It was further shown that these charge fluctuations strongly modulate the potential barrier for the conducting ion at the selectivity site due to amplification of electrostatic interactions in long narrow channels of low dielectric constant. These findings have allowed us to model the mean ion transition time through the channel as an ionic escape from the potential well at the selectivity site induced by thermal fluctuations and by modulation of the height of the barrier by stochastic Poisson processes. The proposed model is a Brownian dynamical model of a ‘knock-on’ mechanism [40, 41]. It allows for analytic estimation of transition probabilities in the presence of charge fluctuations, i.e. it allows for analytic estimation of correlations between bulk concentrations and ion currents in charged narrow channels. In particular, it demonstrates the effect of current saturation due to ion concentrations in the bath. The model is of an essentially non-equilibrium character. This last point is worth emphasizing because traditional approaches assume equilibrium rates of hopping between the sites.

The model takes account of the wall fluctuations. This latter feature is very important e.g. for an analysis of the tightly correlated motion at the selectivity site, of the type

discovered in KcsA [42]. Our model allows for analytic estimation of transition rates in the presence of oscillations of channel walls, using our earlier results [43] on escape from periodically driven potentials based on application of the logarithmic susceptibility [44], as will be discussed in detail elsewhere. Such an escape process, assisted by the periodic modulation of the potential barrier by the wall oscillations, can result on its own in selectivity between like ions due to the difference in their diffusion coefficients [45, 46]. However, ultimately the selectivity of the channel has to be incorporated into the model by taking into account the effects of hydration [47] (see also [20] for a discussion of how the hydration effect can be incorporated in our model). It is also worth mentioning that a model taking into account wall fluctuations may account for dissipation of energy in the channel, for self-induced acceleration of the rate of transition of the ion through the channel, and for coupling of the ion motion to the channel gating mechanics. Indeed, in this model, part of the energy induced by a very strong Coulomb interaction between the charged site at the channel wall and the moving ion is stored as the energy of vibrational modes. The latter energy is only partially dissipated by the protein phonon modes. The remaining energy can now be used to modulate the potential barrier for the moving ion in a self-consistent manner to accelerate its transition through the channel. It can also be used to assist the conformational changes that lead to channel gating.

The work in progress contains a plethora of unsolved problems. The immediate extension of the proposed model will be to include more than two levels for the potential at the selectivity site, taking into account positive and negative (or zero) charge at each mouth of the channel. The model can be further refined by including estimates of the return times corresponding to a return of the ion in the channel to the initial bulk solution.

Following the discussion above, we formulate the following general unsolved problems in ion channels:

- (i) The role of the membrane fluctuations.
- (ii) The role of the hydration potential.
- (iii) The role of additional binding sites outside the selectivity filter.
- (iv) The energetics of the ion transition including energy relaxation due to the coupling to the protein phonon modes (wall oscillations).
- (v) The coupling of the ion-wall interaction to the gating mechanism.

We believe that they can all be tackled by extending the model introduced in this paper. In each case, noise and dynamical effects seem to play a crucial role that is only just starting to be elucidated.

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